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I a tify that the attached copy of the request for grant of a Patent (Form 1/77) bears an am nt, effected by this office, following a request by the applicant and agreed to by the Co ler-General.

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Dated 25 July 2006

Patents Form 1/77

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22AUG02 E742803-1 D00032
P01/7700 0.00-0219511.3

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Request for grant of a patent

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1. Your reference ~~GMW/RAC/P19586GB~~ 00388/GB

2. Patent application number *(The Patent Office will fill in this part)*
0219511.3 21 AUG 2002

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*
Norton Healthcare Limited
Albert Basin
Royal Docks
London
E16 2QJ
United Kingdom

Patents ADP number *(if you know it)* 6188221 003

If the applicant is a corporate body, give the country/state of its incorporation United Kingdom

4. Title of the invention
Method of Preparing Dry Powder Inhalation Compositions

5. Name of your agent *(if you have one)*
ELKINGTON AND FIFE

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*
ELKINGTON AND FIFE
PROSPECT HOUSE
8 PEMBROKE ROAD
SEVENOAKS
KENT
TN13 1XR

Martin A. Hay
13 Queen Victoria St
Macclesfield
Cheshire
SK11 6LP

Patents ADP number *(if you know it)* 67004

8/3/5

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of Filing *(day/month/year)*
N/A		

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of Filing *(day/month/year)*
N/A	N/A

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer "Yes" if:*
a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.

See note (d))

Yes

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	-
Description	6
Claim(s)	2
Abstract	-
Drawing(s)	-

10. If you are also filing any of the following, state how many against each item.

Priority documents	-
Translations of priority documents	-
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	-
Request for substantive examination *(Patents Form 10/77)*	-
Any other documents *(please specify)*	-

11. I/We request the grant of a patent on the basis of this application.

Signature: Elkington and Fife

Date: 21 August 2002

12. Name and daytime telephone number of person to contact in the United Kingdom

Dr Gordon Wright
01732 458881

METHOD OF PREPARING DRY POWDER INHALATION COMPOSITIONS

This invention relates to a method of preparing dry powder inhalation compositions, in particular inhalation compositions comprising a pharmaceutically acceptable particulate carrier, a first particulate inhalable medicament and a second particulate inhalable medicament, wherein the proportion of the second medicament is relatively small both to the proportion of the first medicament and to the quantity of carrier in the composition.

The preparation of ternary mixtures of a particulate carrier, a first particulate inhalable medicament and a second particulate inhalable medicament poses particular problems when one medicament is present at a relatively small proportion compared to the other medicament. It is difficult to prepare mixtures which are homogeneous. In addition, small quantities of medicament may sometimes bind to the supposedly inert carrier, which can affect the amount of medicament that is made available to the patient when the formulation is delivered, eg by means of a dry powder inhaler (DPI) device. In such devices, a metered dose of composition comprising one or more active ingredients and an inert carrier, such as lactose, is dispensed into the air stream which is produced by the inspirational effort of the patient. The medicaments and carrier are entrained in this air stream, with only the fine particles of medicament entering the deep recesses of the lung (which is the site of action of the medicament), the inert excipient being deposited either in the mouth or in the upper region of the lungs.

Surprisingly, we have found a new method of producing ternary mixtures, which produces mixtures which are homogeneous and which can be used with suitable dry powder inhalers (for example, the inhaler illustrated in WO 92/10229, to give excellent dose uniformity of and dose reliability of and dispersion of both medicament components in the composition.

According to the invention, we provide a method of preparing a dry powder inhalation composition comprising a pharmaceutically acceptable particulate carrier, a first particulate inhalable medicament and a second particulate inhalable medicament, wherein the proportion of the second medicament is small relative to the proportion of

the first medicament and to the quantity of carrier in the composition, characterised in that the carrier is mixed with a first portion of the first medicament, the resulting mixture is mixed with substantially all of the second medicament to give a pre-mixture and then the remaining portion of the first medicament is mixed with the pre-mixture to give the desired dry powder inhalation composition.

We prefer the first portion of the first medicament to be less than half of the total quantity of the first medicament.

We prefer the first portion of the first medicament to be less than 2 % weight by weight of the total amount of carrier.

Whilst not wishing to be bound by theory, it is believed that a key aspect of the invention is that the first portion of the first medicament should be administered in a sufficient amount to create a monolayer of the first medicament on the carrier.

The amount of medicament to form a close packed monolayer of first medicament on the carrier can be calculated using the following equation:

$$C^{\min} = 2\pi d \frac{(D+d)^2}{\sqrt{3}D^3}$$

where D and d are the volume median diameters (VMD) of the carrier and first medicament respectively. Thus for a carrier with a VMD of approximately 57.5 microns and a first medicament with a VMD of approximately 1.44 microns, $C^{\min} \approx$ 0.1% weight by weight. Thus in blending 2.15 grams of first medicament with 47.72 grams of carrier, the first portion of first medicament to be added would be 0.04772 grams. We prefer the first portion of first medicament to be added using a geometric mixing process.

We particularly prefer compositions in which the carrier is lactose, especially alpha lactose monohydrate. In general, the particle size of the lactose should be such that it can be entrained in an air stream but not deposited in the key target sites of the lung. Accordingly, lactose with a mean particle size of less than 40 microns is generally

excluded. We prefer the carrier to have a VMD of from 50 to 250μm eg from 50 to 60μm or 60 to 90μm or 90 to 150μm.

We prefer the first medicament to be an anti-inflammatory steroid, for example, budesonide.

We prefer the second medicament to be a bronchodilator, in particular a long acting bronchodilator, such as formoterol or a pharmaceutically acceptable salt thereof.

The proportion of first medicament to second medicament by mass will depend on the relative potencies of the medicaments concerned and will generally be known by the skilled person in the art. However, as a guidance, these proportions may be from 5:1 to 100:1.

Characteristically, the proportion of second medicament to carrier will be in the range 10:1 to 10,000.

Example

Preparation of budesonide/formoterol/lactose blends

100:6 and 200:6 microgram budesonide/formoterol blends at 2.5 kilo scale

Blend Strength	Lactose	Budesonide	Formoterol
100:6	2354.25 grms	137.5 grams	8.25 grams
200:6	2373.8 grams	122.5 grams	3.7 grams

Stage 1

A monolayer of budesonide was formed on the lactose crystals employing 0.5 % weight by weight of budesonide. The required amount of lactose and budesonide (see Table) were dispensed into separate stainless steel containers. Half the lactose was placed into a stainless steel mixing container with a lid. A 4 litre container was used

for 1 kilo/2 kilo batches and both 8 litre and 10 litres containers for 2.5 kilo/batches. Any aggregates of budesonide were broken up with a spatula and the active ingredient was gradually added with even distribution over the lactose bed. The remaining lactose was added into the mixing vessel. The mixing vessel was then placed on a Turbula mixer for 10 minutes at gear 3.

Stage 2

The formoterol was added to the pre-blend from stage 1. The required amount of formoterol (see Table) was weighed into a stainless steel beaker. The formoterol was added into the mixing container after breaking up any agglomerates with a spatula. This was added a spatula full at a time ensuring even distribution over the blend. The container was then replaced on the Turbula mixer for 40minutes at gear 3.

Stage 3

The rest of the budesonide was added to the blend. The budesonide was dispensed into a stainless steel beaker. Half the pre-blend from stage 2 was added into the 3 litre bowl of an aeromatic fielder pma 1 granulator. The budesonide was subsequently added in, carefully ensuring an even disbtribution around the bowl. The remaining pre-blend was added in. The powder was mixed for 15 minutes with a granulator speed of 1500 rpm and a chopper speed of 600 rpm. The blend was discharged from the mixer into a double polythene bag. The blend was poured into a 250 micron sieve assembly and sieved at amplitude 0.65 millimetres using the Retsch sieve shaker.

Ten samples from different spots of the blend were taken for homogeneity analysis for both budesonide and formoterol. All blends were found to contain drugs close to the targets with relative standard deviation (RSD) of drug content < 5% (Table 2).

Table 2: Homogeneity Results for Budesonide and Formoterol Blends.

Batch Number	Budesonide Concentration % w/w			Formoterol Concentration % w/w		
	Target	Actual	% RSD	Target	Actual	% RSD
RD-01-020	4.90	4.9	1.8	0.148	0.152	2.9
RD-01-021	5.5	5.3	2.2	0.330	0.335	4.1
RD-01-022	4.90	4.8	1.3	0.148	0.151	2.2
RD-01-023	5.5	5.3	2.0	0.330	0.336	3.2

After the blend was found to be homogeneous in drug contents, it was then filled in the Ivax multidose DPI (MDPI), a DPI devise based on that disclosed in WO92/10229. The inhalers that contained the formulation were then tested for pharmaceutical performance under conditions specified in European Pharmacopoeia (2001). The drug per actuation (DPA) was measured using a dose unit sampling unit whilst fine particle dose (FPD) and fine particle fraction (FPF) were measured using a 5-stage liquid impinger

The compositions gave excellent dose uniformity with mean DPA close to label claim for both medicaments when used in association with the device of WO 92/10229, with a good proportion of fine particles of both drugs (Tables 3 & 4).

Table 3: Pharmaceutical Assessment Results for the blends for the delivery of 100 mcg budesonide (Bud) and 6 mcg formoterol (EML)

Batch No.	Device 1		Device 2		Device 3	
% FPF	**BUD**	**EML**	**BUD**	**EML**	**BUD**	**EML**
RD-01-021	49.5	34.5	49.5	35.0	49.0	36.0
RD-01-023	50.5	38.5	52.5	39.0	51.0	37.5
FPD µg						
RD-01-021	54.9	2.4	52.3	2.3	52.4	2.4
RD-01-023	54.6	2.5	55.8	2.5	55.7	2.5
Mean DPA						
RD-01-021	111.8	6.5	105.6	6.6	108.9	6.7
RD-01-023	105.8	6.3	108.6	6.5	110.6	6.6

Table 4: Pharmaceutical Assessment Results for the blends for the delivery of 200 mcg budesonide (Bud) and 6 mcg formoterol (EML)

Batch No.	Device 1		Device 2		Device 3	
% FPF	**BUD**	**EML**	**BUD**	**EML**	**BUD**	**EML**
RD-01-020	51.5	38.0	52.0	38.0	48.0	33.5
RD-01-022	49.0	35.5	52.5	37.5	47.0	34.0
FPD µg						
RD-01-020	111.2	2.4	113.5	2.5	99.7	2.1
RD-01-022	97.0	2.2	103.0	2.2	95.9	2.1
Mean DPA						
RD-01-020	212.0	6.3	225.6	6.7	216.3	6.5
RD-01-022	217.2	6.5	206.2	6.1	206.7	6.2

CLAIMS:

1. A method of preparing a dry powder inhalation composition comprising a pharmaceutically acceptable particulate carrier, a first particulate inhalable medicament and a second particulate inhalable medicament, wherein the proportion of the second medicament is small relative to the proportion of the first medicament in the composition and to the quantity of the carrier in the composition, characterised in that the carrier is mixed with a first portion of the final medicament, the resulting mixture is mixed with substantially all of the second medicament to give a pre-mixture and then the remaining portion of the first medicament is mixed with the pre-mixture to give the desired dry powder inhalation composition.

2. A method according to Claim 1, wherein the first portion of the first medicament is less than half of the total quantity of the first medicament in the composition.

3. A method according to Claim 1 or Claim 2, wherein the first portion of first medicament is less than 2% weight by weight of the total amount of carrier.

4. A method according to any of Claims 1 to 3, wherein the first portion of first medicament is sufficient to create a monolayer of the first medicament on the carrier.

5. A method according to any one of the preceding Claims, wherein the carrier is lactose.

6. A method according to any one of the preceding Claims, wherein the first medicament is an anti-inflammatory steroid

7. A method according to any one of the preceding Claims, where the medicament is budesonide

8. A method according to any one of the preceding Claims, where the second medicament is a bronchodilater.

9. A method according to any one of the preceding Claims, where the second medicament is formoterol or a pharmaceutically acceptable derivative thereof.

10. A method according to any one of the preceding Claims, wherein the ratio of first medicament to second medicament by weight is from 5:1 to 100:1.